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MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
OLSON, ERIC	

ART UNIT	PAPER NUMBER
1623	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/780,447	VARGEESE ET AL.	
	Examiner	Art Unit	
	Eric S. Olson	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *1-4,7-9,12-14 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5,6,10,11,15,16,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *September 9, 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

This application is a continuation in part of 10/427160, filed April 30, 2003, currently pending, which is a continuation in part of PCT/US02/15876, filed May 17, 2002, which claims benefit of provisional applications: 60/292217, filed May 18, 2001, 60/306883, filed July 20, 2001, 60/311865, filed August 13, 2001, and 60/362016, filed March 6, 2002. This application is also a continuation-in-part of PCT/US03/05346, filed February 20, 2003, and PCT/US03/05028, filed February 20, 2003, which claims benefit of the following provisional applications: 60/358580, filed February 20, 2002, 60/363124, filed March 11, 2002, 60/386782, filed June 6, 2002, 60/406784, filed August 29, 2002, 60/408378, filed September 5, 2002, 60/409293, filed September 9, 2002, and 60/440129, filed January 15, 2003.

Election/Restrictions

Applicant's election with traverse of group II, claims 5-6, 10-11, 15-16, and 20-21, drawn to compounds of formula **119** or **121**, comprising a biologically active molecule and a cluster glycosyde moiety, filed October 19, 2006, is acknowledged. Because no arguments were given as to the supposed defects in the requirement for restriction, the election is treated as an election without traverse and the requirement for restriction is made **FINAL**.

Claims 1-4, 7-9, 12-14, and 17-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no

allowable generic or linking claim. Election was made with traverse in the reply filed on October 19, 2006.

Claims 5-6, 10-11, 15-16, and 20-21 are pending in this application and examined on the merits herein.

Specification

The abstract of the disclosure is objected to because it is not representative of the claimed subject matter. The abstract recites, "**cholesterol, folate, galactose, galactosamine, N-acetyl galactosamine, PEG, phospholipid, peptide and human serum albumin (HSA)** derived conjugates of biologically active compounds," while the claims are drawn solely to **galactosamine and N-acetyl galactosamine** conjugates of biologically active molecules. Appropriate correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 20-21 are objected to because of the following informalities: the claims recite the phrase, "comprises **and** sense strand and an antisense strand." This phrase is likely meant to be, "comprises **a** sense strand and an antisense strand." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-6, 10-11, 15-16, and 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a conjugate comprising a specific biologically active molecule such as a VEGF antagonist or a small interfering RNA (siRNA) and a specific linker W such as a polyethylene glycol, does not reasonably provide enablement for any compound of the claimed structures comprising any biologically active molecule and any linker. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to *In re Wands*, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a chemical compound.

The state of the prior art: The current state of the art in organic synthesis is such that many diverse chemical structures may be synthesized by one skilled in the art with a sufficient amount of experimentation. Conjugates of the type claimed, in which various molecules are attached to an inert linker such as polyethylene glycol, are well known in the art. However, the full range of conceivable linker molecules, covering any possible chemical structure, has not been tested.

Many biologically active molecules are known in the art. These include, but are not limited to, nucleic acids including DNA, mRNA, tRNA, ribosomal RNA, and ribozymes, proteins including enzymes, receptors, receptor ligands, structural proteins and transcription factors, for example, carbohydrates, including glycoproteins and glycolipids, steroids and other hormones, various small molecule natural products, synthetic biologically active pharmaceutical compounds, and a wide diversity of other molecules which produce some effect *in vivo*. It is also known that the current state of the art has not exhaustively cataloged each and every biological molecule or devised ways of delivering all such molecules to any appropriate biological target.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Biological molecules exert a wide variety of effects *in vivo*. The method by which a biologically active compound is delivered often has a profound impact on the magnitude and character of its effect, due to such factors as the ease of adsorption, extent of *in vivo* metabolism or clearance, and availability at specific tissues or cell types. Different kinds of molecules are subject to vastly different *in vivo* responses, including metabolism, cellular uptake, and immune

attack. Therefore the construction of a conjugate of a biologically active molecule with a targeted delivery vehicle is highly unpredictable.

The Breadth of the claims: The instant claims are extremely broad, covering any molecule with any biological activity whatsoever. This includes **any** compound which interacts in any way with **any biological system** *in vivo*.

The amount of direction or guidance presented: Applicant's specification discloses that compounds of this type, in which RNA is the biologically active molecule, are useful for delivering ribozymes, aptamers, small interfering RNAs, and other biologically active nucleic acids to cells *in vivo*. The specification does not disclose an exhaustive description of which non-nucleotide compounds may be usefully delivered in this manner.

The presence or absence of working examples: Examples of cluster-glycoside-conjugated nucleic acids are given, (e.g. figures 32-36) and methods for their synthesis are provided. Conjugates of a representative sample of all possible biologically active molecules are not provided.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the understanding of all biological molecules. See MPEP 2164.

The quantity of experimentation necessary: One of ordinary skill in the art, in order to practice the claimed invention with the full range of biologically active compounds beyond the meager number disclosed in the specification would be required to test potential compounds *in vivo* to determine whether a particular compound is

biologically active. According to the 2006 Chemical Abstracts catalog, The Chemical Abstracts Registry contains entries for approximately 26 million compounds, all of which are potentially included in the claimed invention if they happen to exert any activity *in vivo*. For most compounds, it is unknown whether or not they exert a biological activity. Gathering this data for every compound known to man would involve *in vitro* screening of an enormous diversity of chemical compounds against every known biological target, or *in vivo* testing in multiple experimental systems including various plants, animals, bacteria, and protozoa, for example. *In vitro* testing requires that the compounds to be tested be synthesized and subjected to an appropriate screening method against every possible biological target. *In vivo* testing requires extensive observation, under diverse conditions, of a large number of biological models representing all kingdoms of life in order to observe the myriad biological activities which could be produced by the various compounds tested. As described earlier, synthesis of diverse chemical structures requires novel and unpredictable experimentation in order to develop suitable synthetic methods. *In vivo* animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose even greater ethical and regulatory burdens, as well as additional difficulty locating subjects. Because of the subtlety of many biological activities, especially those involving ligand-receptor interactions, it is very difficult to generalize results from one

particular compound to other related compounds. Because of the unpredictability of the art and the lack of comprehensive working examples covering any significant portion of the total number of potential biologically active molecules, these animal experiments would need to be repeated thousands of times at least, and involve the maintenance, killing, dissection, and disposal of an extraordinary number of experimental animals, to establish the activity or lack thereof of every possible biologically active compound, thus presenting an a burden of undue experimentation to anyone practicing the invention with the full range of biologically active compounds claimed.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the breadth of the claims and the unpredictability of the art, Applicants fail to provide information sufficient to practice the claimed invention for all biologically active compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-6 and 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (PCT international publication WO90/12096, included with PTO-1449) in view of Connolly et al. (Reference included with PTO-1449) Low et al. discloses that exogenous molecules conjugated to a biotin or folate ligand exhibit improved transport across the cell membrane. (p. 7, lines 5-24) This process takes place through the receptor mediated transmembrane transport of the biotin or folate moiety of the complex. (p. 4, lines 26-30) Various biologically active molecules may be transported in this manner. (pp. 9-11) The method is recognized as being particularly useful for the transport of polynucleotides across the cell membrane. (p. 6, lines 16-20) The complexes are typically formed by covalently attaching the exogenous molecule to the receptor-activating moiety by any common linker. (p. 12, lines 1-25) Low et al. does not specifically disclose the compounds of instant claims 5-6 and 15-16.

Connolly et al. discloses that synthetic cluster glycosides containing three N-acetylgalactosamine ligands (p. 940, diagram 1, bottom of page) bind to cell surface receptors on rabbit hepatocytes and are taken up into the cells by endocytosis. (p. 939, right column, third paragraph)

It would have been obvious to one of ordinary skill in the art at the time of the invention to produce a conjugate comprising a biologically active molecule conjugated to a cluster of three N-acetylgalactosamine residues by the trivalent linkers of formulas 119 and 121, attached with the linkers of instant claims 15-16. One of ordinary skill in the art would have been motivated to make this modification because Low et al. discloses that conjugation of a biologically active molecule to a molecule which

undergoes transport across the cell membrane improves the uptake of the biologically active molecule into its target cells, and because Connolly et al. discloses that a trivalent cluster glycoside of similar structure to the claimed compounds is taken up specifically by hepatocytes, making it a useful targeting moiety for delivery of biologically active compounds to the liver. One of ordinary skill in the art would reasonably have expected success because the selection of particular linking groups to conjugate two known molecules is well within the ordinary and routine level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Claims 10-11 and 20-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Low et al. (PCT international publication WO90/12096, included with PTO-1449) in view of Connolly et al. (Reference included with PTO-1449) further in view of Li et al. (PCT international publication WO00/44914, included with PTO-1449) The disclosures of Low et al. and Connolly et al. are discussed in a previous rejection. Low et al. in view of Connolly et al. does not explicitly disclose the specific cholesterol-conjugated compounds of the claimed invention comprising a double-stranded siNA molecule or portion thereof.

Li et al. discloses a double-stranded RNA which acts to specifically inhibit expression of a target gene. (p. 9, lines 13-24, p. 11, lines 20 – p. 12, line 10) One embodiment of this invention is a double-stranded RNA which inhibits expression of a gene required for maintenance of a cancer phenotype, therefore inhibiting cancer cells.

(p. 16, lines 24-31) This dsRNA is reasonably considered to be a siNA molecule according to instant claims 7-9 and 17-19, and also an exogenous molecule according to Low et al.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the compounds of Low et al. in view of Connolly et al. by attaching the dsRNA molecules of Li et al. by the sense strand, as the exogenous molecule described by Low et al. One of ordinary skill in the art would have been motivated to attach the dsRNA in order to improve its delivery into the target cell for therapeutic gene inhibition. One of ordinary skill in the art would reasonably have expected success because the conjugates of Low et al. are already disclosed to be useful for the delivery of nucleic acids.

Thus the invention taken as a whole in *prima facie* obvious.

Summary

No claims are allowed in this application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. Olson whose telephone number is 571-272-9051. The examiner can normally be reached on Monday-Friday, 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Anna Jiang can be reached on (571)272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric Olson
Patent Examiner
AU 1623
11/2/06

Anna Jiang
Supervisory Patent Examiner
AU 1623